Kidney International, Vol. 4 (1973), p. 12–21

Renal vasodilation and uncoupling of blood flow and filtration rate autoregulation

PHILIP G. BAER and L. GABRIEL NAVAR

Department of Physiology and Biophysics, University of Mississippi School of Medicine, Jackson, Mississippi

Renal vasodilation and uncoupling of blood flow and filtration rate autoregulation. Renal vasodilation experiments were conducted in dogs to examine the mechanism by which the kidney continues to autoregulate glomerular filtration rate during decreased blood flow autoregulatory efficiency. Following intra-arterial infusions of acetylcholine, dopamine, papaverine or prostaglandin E_2 (PGE_2), renal blood flow increased by 40 to 100%, intrarenal venous pressure increased by 45 to 120%, and urine flow increased up to fivefold. GFR was not altered significantly except for a decrease observed during papaverine infusion. The magnitude of the diuretic responses was not directly related to either the increase in renal blood flow or the increase in intrarenal venous pressure. Blood flow autoregulatory efficiency during reductions in arterial pressure was decreased to a variable extent and most markedly with acetylcholine. Efficiency of GFR autoregulation was well maintained during vasodilation with acetylcholine, dopamine and PGE_2. Intrarenal venous pressure and glomerular pressure (computed on the basis of minimal preglomerular resistance measurements) were elevated during vasodilation and became more responsive to changes in arterial pressure. The results indicate that while renal vasodilation decreases both pre- and post-glomerular resistances, a net increase in glomerular pressure occurs. The increase in intrarenal venous pressure suggests that proximal tubular pressure increases to offset the increased glomerular pressure. The concomitant changes in intrarenal venous pressure and glomerular pressure during reductions in arterial pressure suggest further that maintenance of effective filtration pressure and thus GFR during vasodilation may be effected by changes in proximal tubular pressure associated with the changes in glomerular pressure.

Vasodilatation rénale et dissociation de l'autorégulation du débit sanguin rénal et du débit de filtration. Des expériences de vasodilatation rénale ont été réalisées chez des chiens afin d'étudier le mécanisme par lequel le rein continue à réguler le débit de filtration glomérulaire alors que l'efficacité de la régulation du débit sanguin est diminuée. Après la perfusion intra-artérielle d'acetylcholine, de dopamine, de papavérine ou de prostaglandine E_2 (PGE_2), le débit sanguin rénal a augmenté de 45 à 120% et le débit urinaire augmenté jusqu'à 5 fois. Le débit de filtration glomérulaire n'a pas été significativement modifié à l'exception d'une diminution observée au cours de la perfusion de papavérine. Aucune corrélation n'a pu être établie entre l'importance de la réponse diurétique et l'augmentation du débit sanguin rénal d'une part et l'augmentation de la pression veineuse intra-rénale d'autre part. L'efficacité de l'autorégulation du débit sanguin rénal en présence de diminutions de la pression artérielle a été diminuée de façon variable, la diminution la plus importante a été observée avec l'acetylcholine. L'efficacité de l'autorégulation du débit de filtration glomérulaire a été bien maintenue au cours de la vasodilatation par l'acetylcholine, la dopamine et le PGE_2. La pression veineuse intra-rénale et la pression glomérulaire (calculées à partir de mesures de la résistance pré-glomérulaire minimale) ont été plus influencées par les variations de la pression artérielle dans les situations de vasodilatation. Le résultat de ces expériences indique qu'alors que la vasodilatation rénale diminue à la fois les résistances pré et post glomérulaires la pression glomérulaire augmente. L'augmentation de la pression veineuse intra-rénale suggère que la pression tubulaire proximale augmente pour compenser l'augmentation de la pression glomérulaire. Les modifications concomitantes de la pression veineuse intra-rénale et de la pression glomérulaire au cours des réductions de la pression artérielle indiquent que le maintien d'une pression effective de filtration, et donc du débit de filtration glomérulaire, au cours de la vasodilatation est effectué par une modification de la pression tubulaire proximale associée aux changements de la pression glomérulaire.

Recent reports have shown that most vasodilating agents, when infused into the renal artery, do not alter the glomerular filtration rate (GFR) although the total resistance to renal blood flow (RBF) is reduced [1–6]. In contrast, papaverine is reported to cause a decrease in GFR [1, 7, 8] while some investigators [9] report that it is increased by dopamine. Also, it has been demonstrated that the capability to autoregulate the GFR in response to reductions in arterial pressure can continue undiminished [1, 10] despite a greatly reduced ability to autoregulate RBF, although the abolition of GFR autoregulation can sometimes occur during acetylcholine infusion [11].

Although GFR is not usually elevated with vasodilation, urine flow and electrolyte excretion are markedly increased [1–5, 8, 12–14], and become more sensitive to changes in renal arterial pressure [1, 10, 15]. The responsible mechanism

Received for publication November 22, 1972;
received in revised form March 6, 1973.

for the reduction in net tubular fluid reabsorption remains incompletely understood. Some investigators have suggested a direct effect of certain vasodilators to inhibit transport of sodium and water out of the tubules or to alter permeability and thus allow increased backflux from interstitium to tubule lumen [2, 8, 13, 16, 17]. Others suggest that the decrease in reabsorption is secondary to changes in the net Starling forces which govern uptake by the peritubular capillaries; as a result, there occurs an elevation of pressure subsequent to reduced resistance to blood flow and/or a reduced peritubular capillary colloid osmotic pressure resulting from the decreased filtration fraction [1, 3, 12, 18, 19]. Accompanying the elevation in peritubular capillary blood pressure is an increase in proximal tubular fluid pressure [20, 21] and an increase in renal lymph formation [22] which indicates an increased renal interstitial pressure.

It has sometimes been assumed that the absence of a change in GFR also indicates an absence of a change in glomerular pressure; consequently, vasodilators that do not alter GFR have been considered to cause appropriate alterations in both afferent and efferent arteriolar resistance such that glomerular pressure stays constant [5, 11, 14]. However, the reports showing that proximal tubular pressure is also affected by vasodilators [20, 21] necessitate a more stringent evaluation of changes in segmental resistances in response to vasodilators.

The mechanism by which GFR continues to be autoregulated during vasodilation while RBF becomes a nearly passive function of arterial pressure is not apparent. In normal conditions, constancy of both GFR and RBF during changes in renal perfusion pressure has been thought to be achieved by alterations in resistance of the afferent arterioles [20, 23]. According to this concept, GFR is autoregulated because glomerular pressure is also maintained relatively constant during changes in arterial pressure. However, because of our previous finding that the two autoregulatory phenomena can be uncoupled during vasodilation [1], it was deemed necessary to re-examine the possible mechanisms of GFR autoregulation during both normal and vasodilated states. A technique based on the concept of minimal pre-glomerular resistance as previously presented [23] has been utilized to evaluate segmental vascular resistances and to estimate mean glomerular pressure at several arterial pressures in control states and during vasodilation. In addition, these studies have allowed a comparison of the relative effects of the various vasodilators on renal blood flow, intrarenal venous pressure, and urine flow; thus, they are germane to the mechanism of vasodilator diuresis. Finally, the nature of this study allows an evaluation of the possible role of filtration equilibrium in the regulation of glomerular dynamics in the dog.

Methods

Experimental preparation. Experiments were performed on 18 dogs weighing 17 to 30 kg and anesthetized with 30 mg/kg sodium pentobarbital. The right femoral artery and left jugular vein were catheterized to permit measurement of aortic blood pressure, sampling of arterial blood, and infusion of solutions. A tracheotomy was performed and artificial respiration was maintained when necessary.

As previously described [1, 23], the left renal artery and vein, ureter, and gonadal vein were freed from surrounding tissue through a left flank incision. The ureter was catheterized and timed urine samples were collected in calibrated tubes. The gonadal vein was catheterized with an 18-gauge Teflon needle catheter which was advanced to the renal vein to permit collection of renal venous blood. A 15-gauge needle was passed through the dorsal body wall to permit retrograde catheterization of the renal vein with a 20-gauge Teflon needle catheter. This catheter was advanced until a sudden rise in pressure and the appearance of pressure pulsations indicated that it had entered the region of the junction of the interlobar and arcuate veins [23, 24]. The catheter was attached to a Statham pressure transducer for measurement of intrarenal venous pressure (IVP).

A flow transducer was placed on the renal artery adjacent to the aorta to monitor RBF with a Carolina Medical Electronics square-wave electromagnetic flowmeter. Distal to the transducer, a plastic and adjustable occluder was placed on the artery so that renal arterial pressure (RAP) could be set at any level equal to or below aortic pressure. It the artery was too short to accommodate the occluder, an adjustable clamp was placed on the aorta between the left and right renal arteries. After determination of normal RBF, a 20-gauge Teflon needle catheter, connected to a Harvard syringe pump and to a Statham pressure transducer, was inserted into the renal artery distal to the occluder to permit measurement of RAP and infusion into the renal artery. Isotonic saline was continuously infused at 0.2 ml/min through this catheter to prevent clotting.

After collection of control urine and blood samples, a priming dose of polyfructosan (Inutest, Laevosan-Gesellschaft, Austria) was given, followed by a continuous infusion to establish appropriate plasma levels for determination of GFR. A 40-minute equilibration period was allowed before collecting samples.

Experimental protocol. 1) *Control measurements.* Renal arterial pressure was decreased by adjusting the occluder from control aortic pressure to 30 mm Hg in steps of 15 to 20 mm Hg. At each RAP level, adequate time was allowed for blood flow autoregulation to occur. Arterial and renal venous blood samples were collected, and RAP, IVP and RBF were recorded. The renal artery was totally occluded for 10 seconds after measurements were taken at 30 mm Hg to determine the zero blood flow reference level. The occluder was then released and 10 to 15 min were allowed for re-establishment of control conditions.

2) *Measurements during vasodilation.* The renal arterial saline infusion was replaced by an isotonic saline solution containing one of the following: acetylcholine chloride

(Matheson, Coleman and Bell), infused at a rate of 0.25 mg/min in a volume of 0.1 ml/min (4 dogs); papaverine HCl (Eli Lilly and Co.), infused at a rate of 6 mg/min in a volume of 0.2 ml/min (4 dogs); dopamine (3-hydroxytyramine HCl, Sigma Chemical Co.), infused at a rate of 1 to 1.5 μg/kg/min in a volume of 0.1 ml/min (5 dogs); prostaglandin (PGE_2, courtesy of Dr. J. Pike, The Upjohn Co.), infused at a rate of 1.0 μg/kg/min in a volume of 0.1 ml/min (5 dogs).

After a maximum increase in RBF had been achieved, urine samples and arterial and renal venous blood samples were collected and RAP, IVP and RBF were recorded. The occluder was then adjusted to decrease RAP in steps of 15 to 20 mm Hg, and sampling and measuring procedures were repeated at each RAP level. After the zero RBF reference check, the occluder was released, vasodilator infusion was replaced by saline, and a period of 20 to 40 min was allowed for original control values to be achieved. Recovery was usually quite good except for the experiments in which papaverine was infused.

3) *Urine flow measurements.* Following recovery from control measurements, and prior to infusion of vasodilator, two to four timed urine samples were collected. The infusion of vasodilator was begun immediately thereafter, and a second set of two to four urine samples was collected after RBF and urine flow reached steady levels. Urine flow measurements were not included in the study if vasodilator infusion caused arterial pressure to decrease more than 10 mm Hg below control. Since urine samples were not quantitatively collected during renal arterial constriction, this portion of the study is restricted to the response of urine flow to vasodilation at control arterial pressures.

4) *Ureteral occlusion.* Following recovery of the preparation from vasodilator infusion, diuresis was produced by rapid infusion of 350 ml of an isotonic mannitol solution (6.0 g/100 ml) followed by sustaining infusion at 2 to 3 ml/min. The ureteral catheter was attached to a T-tube connected to a long vertical catheter and a Statham pressure transducer. This allowed formation of urine up the vertical catheter until sufficient hydrostatic pressure was generated to stop urine flow. This maximum ureteral pressure was measured, arterial and renal venous blood samples were collected, and RBF, IVP and RAP were recorded.

The renal arterial infusion of saline was then replaced by the vasodilator solution used earlier in the experiment. This was infused at the prior rate for a period of time equal to that required to produce a maximal response in the nonoccluded preparation. Measurements of ureteral pressure, RBF, IVP and RAP were repeated.

5) *Instrument calibration.* Following completion of the ureteral occlusion measurements, the renal artery was catheterized without disturbing the flow transducer. Timed blood flow collections were measured in a graduated cylinder to determine the sensitivity of the flow transducer. Upon termination of the calibration, the kidney was excised, drained and weighed.

Statham pressure transducers were periodically calibrated against a mercury manometer and checked against each other.

Analysis of samples. Plasma concentrations of polyfructosan were determined using an automated anthrone method [1, 23]. Colloid osmotic pressure of arterial blood was measured by a direct method using a membrane osmometer mounted on a Statham pressure transducer [23]. Hematocrits were obtained with microhematocrit capillary tubes. Renal plasma flow was (RPF) calculated from the RBF as determined by the electromagnetic flowmeter according to the formula:

$$RPF = RBF \times (1 - Hct) \tag{1}$$

Inutest (In) extraction data were utilized for the measurement of GFR according to the formula:

$$GFR = RPF \times (In_a - In_v)/In_a \tag{2}$$

where In_a and In_v are the arterial and renal venous Inutest concentrations. The advantages of this method for determining GFR have been discussed in some detail previously [23, 25].

Analysis of data. To provide more uniform results, RBF, GFR and urine flow were expressed as ml/min/g of kidney wt. Intrarenal resistance (IRR) was calculated from the formula:

$$IRR = \frac{RAP - IVP}{RBF}. \tag{3}$$

The resistance terms have the units mm Hg/(ml/min · g) and hereafter will be designated resistance units (RU). Minimal IRR (IRR_m) was defined as the resistance at a RAP (50 to 60 mm Hg) just below the autoregulatory range. Changes in IRR were considered to be primarily due to active response of the smooth muscles of the pre- and postglomerular vessels, while changes in venous resistance (VR) calculated as:

$$VR = \frac{IVP}{RBF} \tag{4}$$

were considered to result primarily from passive factors. During the stop-flow phase of the experiment, the presence of a negligible arteriovenous concentration difference for Inutest was taken as evidence that GFR was at or very near zero. Under this condition, as has previously been discussed [23], it was assumed that the sum of the plasma colloid osmotic pressure and the maximal ureteral pressure was equal to glomerular pressure (GP_{sf}). It should be emphasized that this value for GP is not to be considered as an estimate of normal GP. It has been shown previously that this condition produces a low level of afferent resistance, termed the minimal afferent resistance (AR_m) and calculated as:

$$AR_m = \frac{RAP - GP_{sf}}{RBF}. \tag{5}$$

By infusing vasodilators during this stop-flow phase, it was possible to determine whether this maneuver caused any additional decrease in IRR and AR_m.

The unique advantage of obtaining a value for minimal afferent resistance is related to the calculation of changes in segmental renal resistances during changes in RAP. For any level of RAP, the afferent resistance (AR) was calculated by obtaining the difference between the IRR for that arterial pressure and IRR_m, and adding this difference to AR_m:

$$AR=(IRR-IRR_m)+AR_m. \quad (6)$$

Glomerular pressure was obtained by calculating the pressure drop across the pre-glomerular vessels (AR × RBF) and subtracting this value from RAP.

$$GP=RAP-(AR\times RBF). \quad (7)$$

After arriving at a value for GP, efferent resistance (ER) was calculated:

$$ER=\frac{GP-IVP}{RBF-GFR}. \quad (8)$$

These calculations were incorporated into a PDP-9 digital computer program and data from individual experiments at several RAP levels were analyzed during control conditions and during vasodilator infusion. In addition the same calculations were done on four "idealized" experiments reconstructed from the mean data of the four different experimental groups. Treatment of the data in this manner made it possible to estimate the effects of the vasodilators on the afferent arteriolar and efferent arteriolar resistance segments, as well as on IRR. In addition, we were able to evaluate the changes in glomerular pressure occurring during RAP changes under control conditions and during infusion of vasodilators. By using the intrarenal venous pressure as an estimate of peritubular capillary pressure, the effects of changes in arterial pressure alone or in conjunction with vasodilator infusion on the venous resistance component were also evaluated.

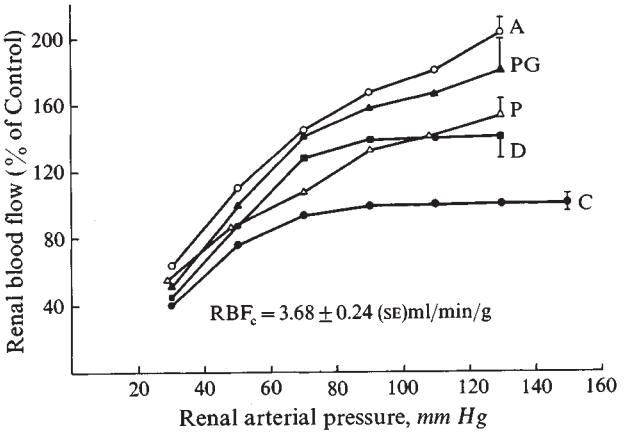

Fig. 1. *Effect of changes in renal arterial pressure on renal blood flow in the control state and during infusion of vasodilators.* The curves are labelled according to vasodilator being used (C = control, D = dopamine, P = papaverine, PG = PGE_2, A = acetylcholine) and standard errors are designated. Overall control RBF at 100 mm Hg is given.

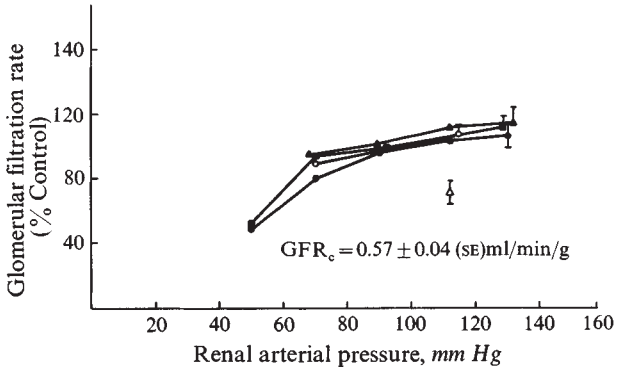

Fig. 2. *Relationships between renal arterial pressure and GFR in control conditions* (•) *and during infusion of dopamine* (▪), *papaverine* (▵), *PGE_2* (▴) *and acetylcholine* (○). Control GFR at 100 mm Hg is shown and other values are expressed as % of control.

Results

Renal blood flow. The response of RBF to changes in RAP during control conditions and infusion of the four vasodilators is shown in Fig. 1. These mean curves were constructed as follows: from the control arterial pressure–blood flow relationship of each experiment, the RBF at 100 mm Hg RAP was determined and designated control RBF (RBF_c). Other blood flows during the control and vasodilated states were then expressed as a percent of RBF_c. The average RBF_c is also shown in Fig. 1 and is the composite from the mean values of the four groups. As evident from Fig. 1, all four agents caused substantial increases in RBF varying from 40% to 100% above control, and RBF was elevated over the entire arterial pressure range examined. However, the effects on RBF autoregulatory efficiency were variable with the dopamine infusions decreasing autoregulatory capability only slightly and the acetylcholine infusions resulting in a pressure-flow relationship most indicative of a passive vascular bed.

Glomerular filtration rate. The responses of GFR to changes in RAP during control conditions and during infusion of vasodilators are shown in Fig. 2. The normalized curves were constructed in the same manner as described for the blood flow curves. The mean RAP-GFR relationship also demonstrated excellent autoregulatory efficiency with values ranging from 96% of GFR_c at 90 mm Hg to 107% of GFR_c at 130 mm Hg. With decreases in RAP to 70 mm Hg, GFR had decreased to 80% and proportionately to a greater extent than the RBF as has been described [11]. At an arterial pressure of 50 mm Hg, GFR had decreased only to 47% of GFR_c.

The responses of GFR to vasodilator infusion contrasted markedly with that of RBF in that a significant

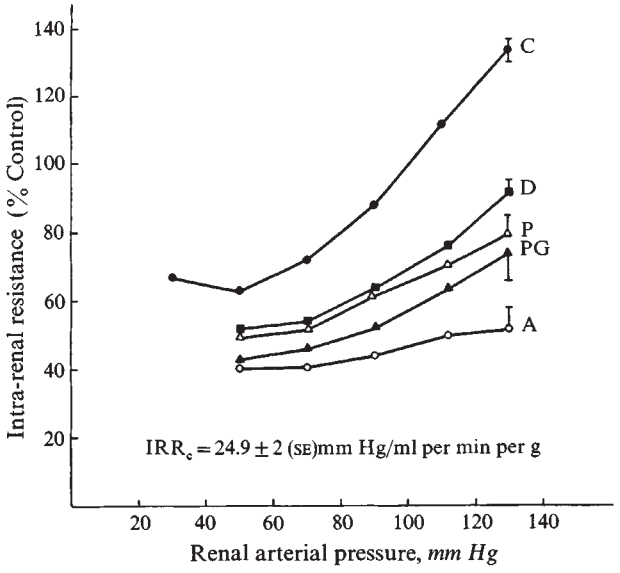

Fig. 3. *Changes in intrarenal resistance in response to gradated reductions in renal arterial pressure during control periods and during infusions of vasodilators.* Curves designated as in Fig. 1.

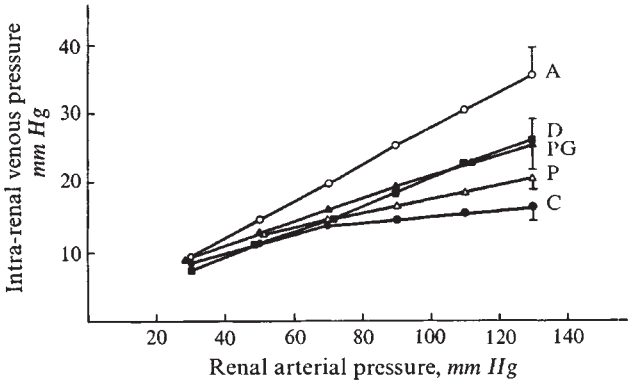

Fig. 4. *Relationships between renal arterial pressure and intrarenal venous pressure obtained in control conditions and during infusion of designated vasodilators.*

increase in GFR was not observed with any of the vasodilators. Additionally, despite the fact that there were substantial differences in RBF autoregulatory efficiency during vasodilator infusion, the RAP–GFR relationship was essentially unchanged from the control relationship during infusions of acetylcholine, dopamine and PGE_2. Papaverine infusion decreased GFR to approximately 60% GFR_c as previously documented [1]. The use of this agent was associated with a greater degree of variability in the data and the decrease in GFR was not generally reversible. For that reason, only a single pooled data point is presented.

Intrarenal and venous resistance. Fig. 3 depicts the effects of alteration in RAP on IRR during control conditions and during vasodilator infusions. The normalized curves were again constructed as previously described. The control relationship demonstrates that as RAP was lowered, IRR decreased from 134% IRR_c at 130 mm Hg down to a minimal value of 62% of IRR_c at a RAP of 50 mm Hg. During infusion of each vasodilator, IRR was reduced to values significantly lower than those in the control relationship over the entire RAP range evaluated. The lowering of minimal IRR at 50 mm Hg below the control IRR_m is considered to result primarily from efferent or postglomerular vasodilation. Dopamine and papaverine decreased this value to approximately 50% of IRR_c while prostaglandin and acetylcholine decreased IRR_m to approximately 40% of IRR_c. It can also be observed that despite the vasodilator infusion, some adjustment of IRR still occurred in response to reductions in RAP. Of the four vasodilators used, acetylcholine was most effective in reducing IRR to near minimal levels even at the higher levels of RAP.

Venous resistance alterations during the control and vasodilated phases of the study were generally quite slight and neither the infusion of vasodilators nor reductions in RAP resulted in significant changes in venous resistance. At a RAP of 130 mm Hg, venous resistance was 4.6 ± SD 0.7 RU during the control phases and was 4.4 ± SD 0.9 RU during the vasodilated phase. There were no perceptible differences in the venous resistance responses to the various vasodilators. With decreases in arterial pressure, venous resistance decreased slightly during both the control and vasodilated phases.

Intrarenal venous pressure and urine flow. The changes in response to decreases in RAP during the control phase and during vasodilation are shown in Fig. 4. At pressures within the autoregulatory range, the control curve exhibits a very slight slope. The slope becomes steeper at the lower arterial pressures. The relationships obtained during vasodilator infusion contrasted in that the IVP values at the higher arterial pressures were increased and the curves approached a more linear configuration. As can be seen, papaverine, dopamine and PGE_2 produced similar effects and acetylcholine produced even greater increases in IVP.

All of the vasodilators caused both an increase in IVP and a diuresis. IVP increased from 16 ± 2 to 25 ± 3 mm Hg while urine flow increased from 1.1 ± 0.3 to 3.9 ± 1 ml/min/100 g kidney wt. When the individual effects of the vasodilators were considered, it was apparent that the responses were quantitatively different, and no consistent proportionality was observed between changes in urine flow and changes in IVP due to vasodilator infusion. Fig. 5 demonstrates that while dopamine and prostaglandin caused similar increases in IVP, urine flow was increased to 145% and 556% of their control values. In contrast, acetylcholine caused an increase of IVP to over 200% of control and the urine flow increased to 475% of control, a response similar to that caused by papaverine and PGE. In addition, comparisons between the diuretic responses and the hyperemic responses also demonstrated that the magnitude of the diuretic response could not be quantitatively accounted for

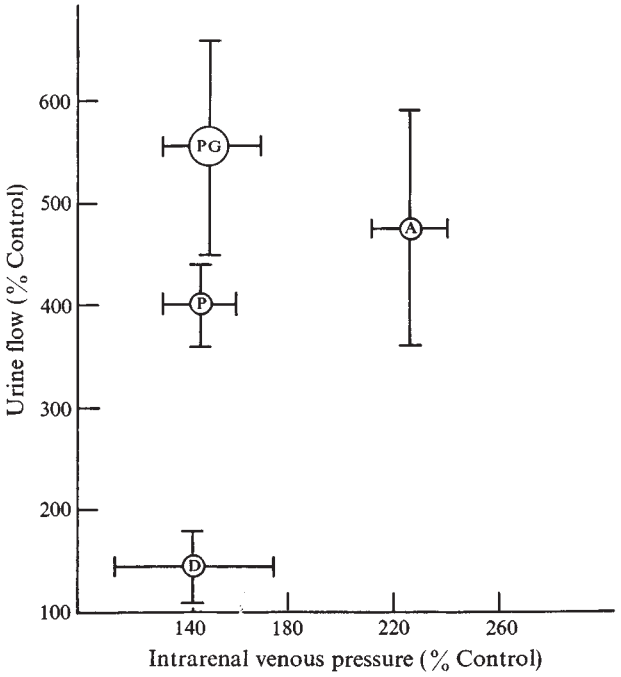

Fig. 5. *Comparison of the effects of various vasodilators on intrarenal venous pressure and urine flow.* For each series of experiments, the relative increase in IVP is plotted against the relative increase in urine flow.

by the magnitude of the hemodynamic responses. Furthermore, while papaverine and acetylcholine caused similar degrees of diuresis, acetylcholine caused a greater increase in RBF and papaverine actually caused a decrease in GFR.

Ureteral obstruction and vasodilator infusion. The third phase of the experiments consisted of administration of a mild isotonic mannitol load followed by ureteral obstruction. The hemodynamic responses were observed when the maximal ureteral pressure had been achieved and arteriovenous inulin concentration differences were obtained to insure that GFR was negligible. To determine if the vasodilators could further decrease the minimal pre-glomerular resistance, the intra-arterial infusions were also repeated during maximal ureteral pressure phases. Table 1 presents the mean values for measured hemodynamic variables and also the resultant calculated values for intrarenal resistance, glomerular pressure, pre-glomerular resistance, and venous resistance. Ureteral occlusion resulted in an increased RBF in all experiments. The calculated glomerular pressure values obtained during maximal ureteral pressure were taken as evidence that pre-glomerular vasodilation was a consistent response of acute ureteral obstruction [25]. The resultant calculated values for minimal preglomerular resistance were, with the exception of the papaverine series, in agreement with values previously obtained [23]. Also, the calculated values for venous resistance during ureteral obstruction were increased two to threefold above the values obtained during the nonobstructed phases. The relatively high value for minimal pre-glomerular resistance obtained in the papaverine series even before re-infusion of the vasodilator indicated that the infusion of papaverine infusion might be associated with certain effects which were not immediately reversible. This finding indicated that calculations based on the papaverine series might not be valid and, for that reason, will not be presented.

The infusion of vasodilators during the obstructed phase resulted in a further slight decrease in intrarenal resistance in all but the dopamine series. For the most part, the additional vasodilation did not occur at pre-glomerular sites. It should be emphasized that this third phase of the experiments was conducted to obtain a value for minimal preglomerular resistance which could then be used in conjunction with data from the control and vasodilated experiments to calculate pre-and postglomerular segmental resistances and mean glomerular pressure.

Table 1. Hemodynamic data from stop flow phase before and during vasodilator infusion

Observation	Prostaglandin		Acetylcholine		Dopamine		Papaverine	
	C	V	C	V	C	V	C	V
Renal arterial pressure, *mm Hg*	142±8	140±10	123±9	112±18	132±18	132±18	135±14	129±11
Renal blood flow, *ml/min · g*	4.9±1.4	5.4±1.6	4.9±1.3	4.7±1.0	4.6±1.6	4.7±1.6	3.9±1.5	4.3±1.6
Intrarenal venous pressure, *mm Hg*	64±18	65±20	49±14	48±17	53±25	55±23	46±19	48±17
Ureteral pressure, *mm Hg*	105±7	103±6	86±9	82±9	89±21	87±23	89±14	84±16
Intrarenal resistance, $\frac{mm\ Hg}{ml/(min \cdot g)}$	17.3±9.1	14.9±3.6	15.8±2.4	14.4±2.8	17.9±2.2	17.0±1.8	22.8±2.6	19.0±1.3
Plasma oncotic pressure, *mm Hg*	20±4	20±4	14±2	14±2	19±3	19±3	17±3	17±3
Glomerular pressure, *mm Hg*	125	123	100	96	108	106	106	101
Preglomerular resistance, $\frac{mm\ Hg}{ml/(min \cdot g)}$	3.5	3.1	4.7	3.4	5.2	5.5	7.4	6.5
Venous resistance, $\frac{mm\ Hg}{ml/(min \cdot g)}$	13.1	12.0	10	10.2	11.5	11.7	11.8	11.2

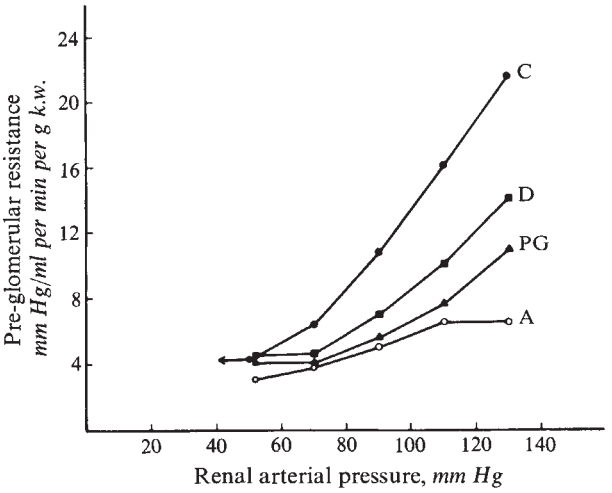

Fig. 6. *Effects on pre-glomerular resistance of reductions in arterial pressure in control state and during infusion of vasodilators.*

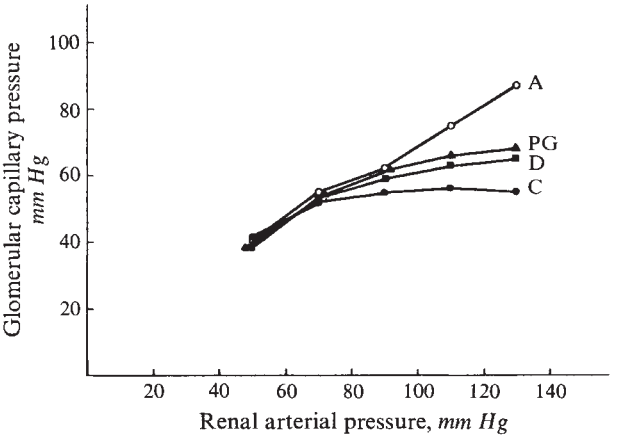

Fig. 7. *Calculated mean glomerular capillary pressure responses to reductions in renal arterial pressure during control state and during infusion of dopamine, PGE_2 and acetylcholine.*

Estimation of glomerular pressure and segmental resistances. The data from control and dilated phases of the experiments were grouped according to the vasodilator infused. For each group, mean values were calculated for RBF, GFR and IVP at RAP between 130 and 50 mm Hg. Using these mean values and those for minimal preglomerular resistance, group mean values were computed for afferent and efferent arteriolar resistances and glomerular capillary pressure as affected by reductions in RAP during control phases and during infusion of vasodilators. Values during vasodilation were normalized so that comparisons could be made against a single set of control values obtained from joint analysis of the control data from all experiments.

Using this technique, the observed relationships between RAP and pre-glomerular resistance during control and vasodilated conditions are shown in Fig. 6. The control curve shows the expected relationship with marked decreases in resistance, within the autoregulatory range and approach of a minimal value at the lower pressures. Dopamine and PGE_2, while causing substantial decreases in resistance did not prevent some additional adjustments in response to decreases in arterial pressure. However, minimal values were reached at a slightly higher arterial pressure. During acetylcholine infusion, preglomerular resistance was lowered to the greatest extent and only slight adjustments were possible with reductions in RAP. In only this series was there evidence that the minimal preglomerular resistance was additionally reduced in response to the vasodilator.

All of the vasodilators caused decreases in efferent resistance also. The mean value for efferent resistance was 10.6 RU with the average from the acetylcholine series being slightly lower (9.2 RU) and the average from the dopamine series being slightly higher (12 RU). Dopamine and PGE_2 produced the same relative effects on efferent resistance, these values decreasing to 72% and 70% of their respective control values. Again, acetylcholine produced the most marked effects with efferent resistance decreasing to 52% of its control value.

Calculations of glomerular pressure indicated that the net result of vasodilation was an increase in glomerular pressure as shown in Fig. 7. Dopamine and PGE_2 caused a moderate increase in glomerular pressure and did not prevent some autoregulation of glomerular pressure in response to reductions in arterial pressure. On the other hand, these calculations indicated that acetylcholine increased glomerular pressure rather markedly and, additionally, there was little evidence of autoregulation of glomerular pressure during reductions of arterial pressure.

The control curve, as previously shown [23], demonstrated typical autoregulatory behavior and the overall mean value for control glomerular pressure obtained in this series of experiments was 55 mm Hg. At arterial pressures below the autoregulatory range, both control and vasodilated glomerular pressures were similar and decreased linearly with further decreases in arterial pressure.

Discussion

In these experiments, the marked renal hyperemia occurring in response to vasodilator infusion was not associated with an increase in GFR. With the exception of papaverine, which caused a decreased GFR, there was no significant alteration in GFR. In addition, while the efficiency of RBF autoregulation in response to reductions in blood pressure was variably reduced, GFR autoregulatory efficiency was not disturbed during infusions of acetylcholine, dopamine and PGE_2. This uncoupling of GFR and RBF autoregulation was most evident during acetylcholine infusion. By utilizing the assumptions and methods presented previously [23] and described in Methods, it was possible to estimate changes in glomerular pressure and segmental vascular resistance in response to reductions in arterial pressure during control and vasodilated states.

Intrarenal resistance alterations during vasodilation. The vasodilator-induced reduction in total renal resistance was shared to some degree by both elements of the pre-venous vasculature. Examination of changes of pre-glomerular resistance, considered to be primarily responsible for the normal autoregulatory adjustments of resistance, suggested that PGE_2 and dopamine partially reduced autoregulatory capability while acetylcholine rendered this vascular segment least capable of responding to changes in arterial pressure. However, during infusion of PGE_2 and dopamine, the afferent arteriolar resistance, while reduced throughout the arterial pressure range over which renal autoregulation occurs, continued to vary with changes of arterial pressure. Thus, continuing autoregulation of RBF during vasodilation was accomplished almost entirely by the residual autoregulatory capability of the afferent arteriolar segments. Evidence was not found to support the possibility that venous compression or alterations in venous resistance contributed significantly to the maintenance of partial renal blood flow autoregulatory ability during vasodilation.

Glomerular filtration during vasodilation. Previous studies have shown that proximal tubular pressure is elevated during vasodilator-induced renal hyperemia [20, 21]. Classically, the observed constancy of GFR implies maintenance of the effective filtration pressure and thus an increase in glomerular pressure. The present results indicate that during vasodilation induced by acetylcholine, dopamine and PGE_2, an increase in glomerular capillary pressure was sufficient to offset the increased proximal tubular pressure, as indirectly estimated from the intrarenal venous pressure measurements. In fact, the calculated increases in glomerular pressure actually exceeded the measured increments in IVP, especially in the acetylcholine series. These discrepancies do not warrant rigorous evaluation because of the quantitative limitations on both the glomerular pressure and the proximal tubular pressure estimates. For example, this technique probably underestimates tubular pressure and might not completely reflect changes in proximal tubular pressure. However, the direct measurements of peritubular capillary pressure in the dog obtained by Knox et al [26] are quite similar to the IVP measurements obtained in this study. Thus it is probably justifiable to conclude that these IVP measurements are valid as an index of peritubular capillary pressure. Fig. 8 depicts the overall pressure and resistance profiles along the renal vasculature calculated for control conditions, vasodilated states and during ureteral obstruction. At an arterial pressure of 110 mm Hg, the increases in IVP were similar to the calculated increases in glomerular capillary pressure in response to the vasodilator infusions. The effects of papaverine could not be evaluated with this technique since valid measurements of minimal afferent resistance were not possible. However, indirect calculations suggested that papaverine produced the greatest relative decrease in efferent resistance and this perhaps resulted in a decreased or unchanged glomerular pressure.

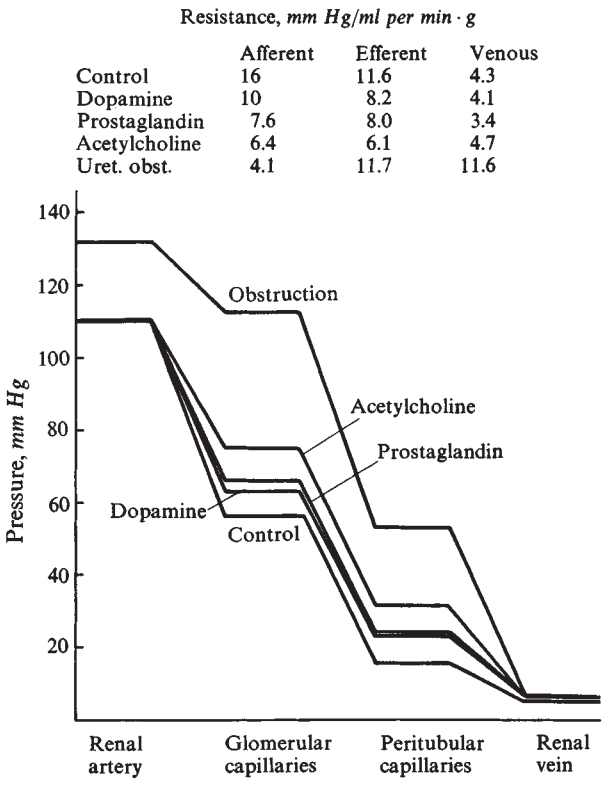

Fig. 8. *Analysis of pressure gradients and resistance elements along the renal vascular bed during control, vasodilator, and ureteral obstruction phases.* For control and vasodilator phases, data were selected at an arterial pressure of 110 mm Hg.

The continuing autoregulation of GFR during vasodilation appears to be dissociated to some extent from afferent arteriolar adjustments. If this were not so, it would be anticipated that GFR autoregulation during dopamine and PGE_2 infusion, for example, would have been much better than during acetylcholine infusion. The data, however, show that GFR autoregulatory efficiency was not diminished during acetylcholine and was essentially the same as during control conditions. At variance with these results, Abe, Dixon and McNay [11] reported loss of GFR autoregulatory behavior during acetylcholine administration. However the pattern obtained in that study suggested that GFR and effective filtration pressure were reduced below control levels following reduction of blood pressure. In the present experiments, GFR was not reduced and continued to exhibit autoregulation. An explanation for this type of autoregulation may be based on the relationships obtained between RAP and intrarenal venous pressure. In the control phase, changes in RAP within the autoregulatory range produced only slight changes in IVP. Presumably, afferent resistance responses plus the higher level of efferent resistance shielded the peritubular capillary network from most of the change in arterial pressure. During vasodilation, the absolute level of resistance across both segments was reduced, as was the ability of the afferent segment to adjust

its resistance with changes in pressure. As a consequence, IVP varied with arterial pressure to a greater extent and in a relatively linear manner, just as it did in the control phases at arterial pressures below 70 mm Hg. To the extent that changes in IVP reflect changes in proximal tubular pressure, the data indicate that changes in glomerular pressure during decreases in RAP in the vasodilated state are accompanied by concomitant changes in proximal tubular pressure. In the acetylcholine series, the changes in estimated glomerular pressure were greater than the IVP changes suggesting an increased effective filtration pressure at the higher arterial pressures. Since GFR was not increased, the possibility exists that proximal tubular pressure increased more than intrarenal venous pressure, especially at the higher pressures obtained with acetylcholine. Because of these limitations, calculations of effective filtration pressure were not considered quantitatively valid. Nevertheless, the data suggest that, under certain circumstances, the steady-state effective filtration pressure can be maintained even in the face of a changing glomerular pressure by accompanying changes in proximal tubular pressure. It is not unlikely that such a mechanism could be responsible for the continuing autoregulation of GFR that occurs in the normal kidney as arterial pressure is increased to levels above the upper limit for RBF autoregulation [27].

Certain aspects concerning the classical concepts [28] related to the nature of glomerular filtration have recently been re-evaluated [29, 30]. In essence, findings of a relatively high filtration fraction and a relatively low glomerular hydrostatic pressure in superficial nephrons of the rat kidney have been interpreted as indicating that filtration equilibrium is normally achieved in the glomerulus. This equilibrium process is thought to occur early within the glomerular capillaries, so that changes in the point at which filtration equilibrium occurs could conceivably play a role in regulating filtration rate. An important prediction of this hypothesis is that an increase in renal plasma flow should be associated with an increase in GFR even if glomerular pressure and effective filtration pressure do not increase. This plasma flow dependence of GFR has been demonstrated in the rat [31]. In the dog, indirect calculations based on stop-flow techniques [23] or molecular sieving analysis [32] have suggested that glomerular pressure in hydropenic conditions is not as low as in the rat. If so, when coupled with recent measurements of superficial efferent protein concentrations [17, 33] in the dog, it would appear that filtration equilibrium does not obtain in the dog, at least during normal hydration and antidiuresis. The present results bear on this point in that marked vasodilation-associated increases in renal plasma flow were not attended by parallel increases in GFR. Also, GFR was not dependent on plasma flow when RAP was reduced and there was no indication that effective filtration pressure was lower during vasodilation than during control conditions. Therefore, the results of this study are interpreted as providing evidence that the process of filtration equilibrium probably does not play a significant role in the control of overall dynamics of glomerular filtration in the dog.

Mechanics of vasodilator diuresis. The central focus of this work was not on the effects of vasodilation on urine flow. However, some of the observed hemodynamic responses bear upon the diuretic response. It is evident that the increase in urine flow is due to decreased tubular fluid reabsorption since diuresis occurred whether GFR was decreased or unchanged. Also, RBF elevation *per se* was not directly associated with the magnitude of diuresis since dopamine increased urine flow only slightly although it increased RBF and intrarenal venous pressure almost as much as papaverine. Other hemodynamic effects were similarly unrelated when examined quantitatively. Acetylcholine produced a much greater increase in intrarenal venous pressure than the other vasodilators, but its diuretic effect was intermediate to that of papaverine and PGE_2. In addition, because acetylcholine increased blood flow more than PGE_2 did, filtration fraction was decreased more by infusion of acetylcholine. Therefore, blood entering the peritubular capillary reabsorptive network would have a lower initial colloid osmotic pressure. Both the greater increase in IVP and the lower initial colloid osmotic pressure in the peritubular capillary during acetylcholine infusion should have produced a diuresis greater than that produced by PGE_2, if alterations in Starling forces governing peritubular capillary uptake are the major determinants of decreased reabsorption during vasodilation. The diuresis was essentially the same. In essence, comparison of the relative hemodynamic and diuretic responses to the various vasodilators lends support to the conclusions of other investigators [2, 8, 13, 16, 17, 34, 35]. Thus while changes in Starling forces may play an important role in mediating the diuretic response, an important variable most likely related to the magnitude of the diuresis is the relative direct effect on reabsorptive mechanisms or tubular permeability.

In conclusion, these experiments suggest that while both pre- and post-glomerular resistances are reduced by vasodilation, net decreases in pre-glomerular resistance usually predominate and glomerular pressure thus increases. Consequently, maintenance of GFR appears to be due, in large measure, to the augmented proximal tubular pressure measured directly by others [20, 21] as indicated by intrarenal venous pressure measurements in this study. With changes in arterial pressure, GFR is normally autoregulated along with renal blood flow and glomerular pressure through adjustments in pre-glomerular resistance. However, during vasodilation, GFR and effective filtration pressure may continue to be autoregulated even in the absence of renal blood flow autoregulation, and it appears that this is effected through concomitant changes in glomerular and proximal tubular pressures.

Acknowledgments

This study was presented in preliminary form at the fall meeting of the American Physiological Society, 1972. It was

supported by Public Health Service Research Grants HE 11428 and HE 11678. Dr. P. G. Baer was a Postdoctoral Research Fellow of the Mississippi Heart Association. Present address: Department of Medicine, Royal Victoria Hospital, Montreal, P. Q., Canada. The authors gratefully acknowledge the assistance of Miss Sue Howard, Mr. Ron Darby and Mrs. Nancy Wright.

Request reprints to Dr. L. G. Navar, Department of Physiology and Biophysics, University Medical Center, Jackson, Mississippi 39216, U.S.A.

References

1. Baer PG, Navar LG, Guyton AC: Renal autoregulation, filtration rate, and electrolyte excretion during vasodilatation. *Am J Physiol* 219:619–625, 1970
2. Cohen RM, Carter MK: The effect of renal arterial infusion of cholinomimetic agents on renal function. *Arch Int Pharmacodyn* 170:473–484, 1967
3. Daugherty TM, Belleau LJ, Martino JA, Earley LE: Inter-relationship of physical factors affecting sodium reabsorption in the dog. *Am J Physiol* 215:1442–1447, 1968
4. Dirks JH, Seely JF: Micropuncture studies on the effect of vasodilators on proximal tubule sodium reabsorption in the dog (abstract). *Clin Res* 15:478, 1967
5. Harvey RB: Effects of acetylcholine infused into renal artery of dogs. *Am J Physiol* 211:487–492, 1966
6. Kiil F, Kjekshus J, Loyning E: Renal autoregulation during infusion of noradrenaline, angiotensin and acetylcholine. *Acta Physiol Scand* 76:10–23, 1969
7. Harsing L, Kover G, Jalyusz J, Toth G, Harza T: Die Wirkung von vasodilatorischen Substanzen (Papaverine, Acethycholine) auf die Nierenfunction. *Pfluger's Arch ges Physiol* 281:346–355, 1964
8. Meyer MB, Goldberg LI: Natriuretic effect of papaverine (abstract). *Fed Proc* 24:258, 1965
9. Lindheimer MD, Lalone RC, Levinsky NG: Evidence that an acute increase in glomerular filtration has little effect on sodium excretion in the dog unless the extracellular volume is expanded. *J Clin Invest* 46:256–265, 1967
10. Gonda A, Wong N, Seely JF, Dirks JH: The role of hemodynamic factors on urinary calcium and magnesium excretion. *Can J Physiol Pharmacol* 47:619–626, 1969
11. Abe Y, Dixon F, McNay JL: Dissociation between autoregulation of renal blood flow and glomerular filtration rate. *Am J Physiol* 219:986–993, 1970
12. Hayslett JP, Domoto DT, Kashgarian M, Epstein FH: Role of physical factors in the natriuresis induced by acetylcholine. *Am J Physiol* 218:880–885, 1970
13. May DG, Garter MK: Unilateral diuresis by infusion of arecoline into renal portal system of hens. *Am J Physiol* 212:1351–1354, 1967
14. Vander AJ: Effects of acetylcholine, atropine and physostigmine on renal function in the dog. *Am J Physiol* 206: 492–498, 1964
15. Willis LR, Ludens JH, Williamson HE: Dependence of the natriuretic action of acetylcholine upon an increase in renal blood flow. *Proc Soc Exptl Biol Med* 128:1069–1072, 1968
16. Stein JH, Reineck JH, Osgood RW, Ferris TF: Effect of acetylcholine on proximal tubular reabsorption in the dog. *Am J Physiol* 220:227–232, 1971
17. Stein JH, Congbalay RC, Karsh DL, Osgood RW, Ferris TF: The effect of bradykinin on proximal tubular sodium reabsorption in the dog: Evidence for functional nephron heterogeneity. *J Clin Invest* 51:1709–1721, 1972
18. Lewy JE, Windhager EE: Peritubular control of proximal tubular fluid reabsorption in the rat kidney. *Am J Physiol* 214:943–954, 1968
19. Carriere S, Friborg J, Guay JP: Vasodilators, intrarenal blood flow and natriuresis in the dog. *Am J Physiol* 221:92–98, 1971
20. Thurau K, Wober E: Zur Localisation der autoregulativen Widerstandsänderungen der Niere. *Pfluger's Arch ges Physiol* 274:553–566, 1962
21. Willis LR, Knox FG: Effect of acetylcholine on hydrostatic pressures in peritubule capillaries in the dog (abstract). *Fed Proc* 31:318, 1972
22. Bell RD: Cortical and medullary canine renal lymph formation during acetylcholine induced renal vasodilation. *Lymphology* 4:74–78, 1971
23. Navar LG: Minimal preglomerular resistance and calculation of normal glomerular pressure. *Am J Physiol* 219:1658–1664 1970
24. Martino JA, Earley LE: Relationship between intrarenal hydrostatic pressure and hemodynamically induced changes in sodium excretion. *Circ Res* 23:371–386, 1968
25. Navar LG, Baer PG: Renal autoregulatory and glomerular filtration responses to gradated ureteral obstruction. *Nephron* 7:301–316, 1970
26. Knox FG, Willis LR, Strandhoy JQ, Schneider EG: Hydrostatic pressures in proximal tubules and peritubule capillaries in the dog. *Kid Internat* 2:11–16, 1972
27. Shipley RE, Study RS: Changes in renal blood flow, extraction of inulin, GFR, tissue pressure and urine flow with acute alterations of renal artery blood pressure. *Am J Physiol* 167:676–688, 1951
28. Gomez DM: Evaluation of renal resistances with special reference to changes in essential hypertension. *J Clin Invest* 30:1143–1155, 1951
29. Brenner BM, Troy JL, Daugharty TM: The dynamics of glomerular ultrafiltration in the rat. *J Clin Invest* 50:1776–1780, 1971
30. Blantz RC, Israelit AH, Rector FC, Seldin DW: Relation of distal tubular NaCl delivery and glomerular hydrostatic pressure. *Kid Internat* 2:22–32, 1972
31. Brenner BM, Troy JL, Daugharty TM, Deen WM, Robertson CR: Dynamics of glomerular ultrafiltration in the rat. II. Plasma flow dependence of GFR. *Am J Physiol* 223:1184–1190, 1972
32. Lambert PP, Verniory A, Gassee JP, Ficheroulle P: Sieving equations and effective glomerular filtration pressure. *Kid Internat* 2:131–146, 1972
33. Knox FG, Willis LR, Strandhoy JW, Schneider EG, Navar LG, Ott CE: Effect of peritubule starling forces in proximal reabsorption following albumin infusion. *Am J Physiol* 223:141–149, 1972
34. Martinez-Maldonado M, Tsaparas N, Eknoyan G, Suki WN: Renal actions of prostaglandins: Comparison with acetylcholine and volume expansion. *Am J Physiol* 222:1147–1152, 1972
35. Massry SG, Ahumada JJ: Renal vasodilatation: Studies on the site of action in the nephron. *Clin Sci* 42:535–543, 1972